

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1 (Currently Amended). A method of treating a tumor, having malignant cells, in a subject, ~~which comprises~~ comprising administering to said subject an ~~effective amount~~ effective to treat the tumor of a composition comprising:

(A) ~~at least one~~ an agent that decreases the [GSH]²/[GSSG] (wherein [GSH] is the concentration of glutathione and [GSSG] is the concentration of glutathione disulfide) ratio in the malignant cells of said tumor, selected from the group consisting of

(i) an agent that oxidizes GSH, or a precursor of said agent; and

(ii) an agent that forms an adduct or a conjugate with GSH, or a precursor of said agent; and

(B) an agent that maintains the decreased [GSH]²/[GSSG] ratio in the malignant cells of said tumor, selected from the group consisting of

(iii) an agent that inhibits the GCS (γ -glutamylcysteine synthetase) enzyme, or a precursor of said agent;

(iv) an agent that inhibits the glutathione reductase (GR) enzyme, or a precursor of said agent; and

(v) an agent that diminishes the precursor of GSH, or a precursor of said agent,

wherein said ~~at least one agent is~~ agents are administered such that a decreased $[GSH]^2/[GSSG]$ ratio is maintained in the malignant cells continuously ~~to said patient for a period of time within the range of from~~ for about 15 to about 75 hours.

2-3 (Cancelled).

4 (Currently Amended). A method according to claim 1, wherein said ~~at least one agent is~~ agents are administered together with a standard chemotherapeutic drug.

5-6 (Cancelled).

7 (Currently Amended). A method according to claim 61, wherein
said ~~at least one agent that oxidizes GSH or a precursor thereof~~ of (i) is selected from the group consisting of disulfiram, hydrogen peroxide, a precursor thereof selected from the group consisting of ascorbic acid and dopamine, α -lipoic acid, oxidized low density lipoproteins (ox-LDLs), and

a quinone selected from the group consisting of duroquinone, an ubiquinone, and β -lapachone, and

~~said at least one agent that forms an adduct or conjugate with GSH, or a precursor thereof, of (ii) is selected from the group consisting of a Michael acceptor or another conjugating agent; arsenic trioxide, diethylmaleate, ethacrynic acid, epothilones A and B, an α,β -unsaturated aldehyde, an unsubstituted or partially substituted quinone, an isoflavone, and a phenol~~

said agent of (iii) is buthionine sulfoximine (BSO);
and

said agent of (iv) is carmustine.

8 (Currently Amended). A method according to claim 721, ~~wherein said at least one agent that forms an adduct or conjugate with GSH, or a precursor thereof, is selected from the group consisting of an isoflavone, an unsubstituted or partially substituted quinone, an α,β -unsaturated aldehyde, and a phenol,~~ wherein said isoflavone is selected from the group consisting of catechin, daidzein, dicumarol, (-)epicatechin, flavopiridol, genistein, β -lapachone, myricetin and rotenone; said unsubstituted or partially substituted quinone is selected from the group consisting of anthraquinone, benzoquinone, 2-methylbenzoquinone, 2,6-dimethyl-benzoquinone, 2,5-dimethyl- benzoquinone, 2,3,5-

trimethyl-benzoquinone, γ -tocopherolquinone and δ -tocopherolquinone; said α, β -unsaturated aldehyde is selected from the group consisting of cinnamaldehyde and a 4-hydroxy-C₅-C₉-alkenal selected from the group consisting of 4-hydroxy-C₅-C₉-pentenal, 4-hydroxy-C₅-C₉-hexenal, 4-hydroxy-C₅-C₉-heptenal, and 4-hydroxy-C₅-C₉-nonenal; and said phenol is selected from the group consisting of curcumin, (-)epigallocatechin-3-gallate, resveratrol, γ -tocopherol, δ -tocopherol, yakuchinone A, and yakuchinone B.

9 (Cancelled).

10 (Currently Amended). A method according to claim 5-1, wherein said ~~synergistic combination composition~~ comprises at least one agent ~~that oxidizes GSH, or a precursor thereof, of (i)~~ and at least one agent ~~that inhibits the GCS enzyme of (iii).~~

11 (Currently Amended). A method according to claim 10, wherein said at least one agent ~~that oxidizes GSH or a precursor thereof of (i)~~ is disulfiram, hydrogen peroxide, a precursor thereof selected from the group consisting of ascorbic acid and dopamine, α -lipoic acid, oxidized low density lipoproteins (ox-LDLs), and a quinone selected from the group consisting of duroquinone, an ubiquinone, and β -

lapachone, and said at least one agent ~~that inhibits the GCS enzyme of (iii)~~ is buthionine sulfoximine (BSO).

12 (Currently Amended). A method according to claim 5-1, wherein said ~~synergistic combination composition~~ comprises at least one agent ~~that oxidizes GSH, or a precursor thereof, of (i)~~ and at least one agent ~~that inhibits the GR enzyme of (iv)~~.

13 (Currently Amended). A method according to claim 12, wherein said at least one agent ~~that oxidizes GSH or a precursor thereof of (i)~~ is disulfiram, hydrogen peroxide, a precursor thereof selected from the group consisting of ascorbic acid and dopamine, α -lipoic acid, oxidized low density lipoproteins (ox-LDLs), and a quinone selected from the group consisting of duroquinone, an ubiquinone, and β -lapachone, and said at least one agent ~~that inhibits the GR enzyme of (iv)~~ is carmustine.

14 (Currently Amended). A method according to claim 5-1, wherein said ~~synergistic combination composition~~ comprises at least one agent ~~that forms an adduct or conjugate with GSH, or a precursor thereof, of (ii)~~ and at least one agent ~~that inhibits the GCS enzyme of (iii), with the exclusion of the combination of As₂O₃ with BSO.~~

15 (Currently Amended). A method according to claim 5-1, wherein said ~~synergistic combination composition~~ comprises at least one agent ~~that forms an adduct or conjugate with GSH, or a precursor thereof, of (ii)~~ and at least one agent ~~that inhibits the GR enzyme of (iv)~~.

16 (Currently Amended). A method according to claim 5-1, wherein said ~~synergistic combination composition~~ is administered continuously to said patient for ~~a period of time within the range of from~~ about 15 to about 75 hours.

17 (New). A method according to claim 1, wherein said $[GSH]^2/[GSSG]$ ratio that is maintained continuously for about 15 to about 75 hours is decreased in an amount such that E is increased by at least 10 mV during said period, wherein $E = E_0 - 30 \log [GSH]^2/[GSSG]$, and wherein E_0 is the standard potential of glutathione.

18 (New). A method according to claim 1, wherein said $[GSH]^2/[GSSG]$ ratio that is maintained continuously for about 15 to about 75 hours is decreased in an amount such that E is increased above E_{CCP} during said period, wherein $E = E_0 - 30 \log [GSH]^2/[GSSG]$, wherein E_0 is the standard potential of glutathione, and wherein E_{CCP} is the redox potential where cessation of cell proliferation occurs.

19 (New). A method according to claim 18, wherein E is increased to above about -200 mV during said period.

20 (New). A method according to claim 19, wherein E is increased to between about -200 mV and -190mV during said period.

21 (New). A method according to claim 7, wherein said Michael acceptor or other conjugating agent is selected from the group consisting of arsenic trioxide; diethylmaleate; ethacrynic acid; epothilone A or B; an α,β -unsaturated aldehyde or ketone; a polyunsaturated fatty acid (PUFA); an unsubstituted or partially substituted quinone; an isoflavone; and a phenol.

22 (New). A method according to claim 11, wherein said at least one agent of (i) is disulfiram and said at least one agent of (iii) is buthionine sulfoximine (BSO).

23 (New). A method according to claim 12, wherein said at least one agent of (i) is disulfiram and said at least one agent of (iv) is carmustine.

24 (New). A method according to claim 1, comprising at least one agent of (i), at least one agent of (iii) and at least one agent of (iv).

Appln. No. 10/621,326

Amd. January 3, 2007

Reply to Office Action of September 1, 2006

25 (New). A method according to claim 24, wherein said at least one agent of (i) is disulfiram, said at least one agent of (iii) is buthionine sulfoximine (BSO) and said at least one agent of (iv) is carmustine.